

Different propensity of cultured aortic valve interstitial cells to uptake native or aggregated low density lipoprotein

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Atherosclerosis is a progressive disease characterized by modified low density lipoprotein (LDL) accumulation in the large artery walls, with subsequent phagocytosis by macrophages, transforming into foam cells, and vascular smooth muscle cells (VSMCs). In particular, native LDL (nLDL) can modify joining to each other giving rise to aggregated LDL (agLDL), which were reported to be internalized more avidly by VSMCs in *in vitro* conditions (1). Here, primarily cultured aortic valve interstitial cells (AVICs) were treated for 3 up to 21 days with 50 mg/ml blood-derived nLDL or agLDL, alone or combined with pro-calcific culture media, to ascertain whether (i) agLDL are taken up more rapidly than nLDL also by AVICs and (ii) treatment with LDL at low, normolipidemic-like concentration can influence AVIC mineralization. Ultrastructurally, LDL uptake was observed exclusively for agLDL-treated AVICs, which were characterized by a lot of endocytic vesicles and intracytoplasmic vacuoles entrapping agLDL particles. Consistently, treatment with agLDL resulted in a significant increase in intracellular amounts of both esterified cholesterol and triglycerides, as chromatographically assayed. Ultrastructural analyses also revealed pro-calcific AVIC degenerative process to occur, consisting in intracellular release of lipidic material and its layering at cell edges, there acting as major hydroxyapatite nucleator (2,3). The extent of pro-calcific effects resulted to be LDL-dependent, being mitigated in the presence of nLDL and exacerbated in the presence of agLDL. These findings were consistent with spectrophotometrical analyses showing decreased calcium amounts in AVIC cultures superstimulated with nLDL and increased mineral content in the counterpart superstimulated with agLDL. Since aortic valve stenosis is considered as a valve atherosclerotic lesion, these preliminary data suggest that avid uptake of agLDL by AVICs might strongly contribute to lipid accumulation within aortic valves, with agLDL possibly affecting subsequent valve tissue mineralization even at concentrations comprised within the normolipidemic range.

References

- [1] Llorente-Cortés et al. (2006) Cholesteryl esters of aggregated LDL are internalized by selective uptake in human vascular smooth muscle cells. *Arterioscler Thromb Vasc Biol* 26: 117-23.
- [2] Ortolani et al. (2010) Pro-calcific responses by aortic valve interstitial cells in a novel *in vitro* model simulating dystrophic calcification. *Ital J Anat Embryol* 115: 135-39.
- [3] Bonetti et al. (2012) Ultrastructural and spectrophotometric study on the effects of putative triggers on aortic valve interstitial cells in *in vitro* models simulating metastatic calcification. *Anat Rec* 295: 1117-27.

Keywords

Aortic valve interstitial cells; aggregated LDL; LDL uptake.